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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/030,417
Filing Date: August 14, 2002
Appellant(s): MULLER ET AL.

Jeffrey S. Melcher
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 09/15/2010 appealing from the Office action mailed 03/23/2010.

**(1) Real Party in Interest**

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The following is a list of claims that are rejected and pending in the application:

Claims 1-17, 20, 24-29, 31-34 and 38-47 are rejected and pending in the application.

**(4) Status of Amendments After Final**

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

**(5) Summary of Claimed Subject Matter**

The examiner has no comment on the summary of claimed subject matter contained in the brief.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

**(7) Claims Appendix**

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

**(8) Evidence Relied Upon**

| | | |
|---|---|---|
| WO98/14174 | Desai et al. | 04-1998 |
| 5858410 | Muller et al. | 01-1999 |

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-17, 20, 24-29, 31-34, and 38-47 remain rejected under 35 U.S.C.103(a) as being unpatentable over Desai et al WO 98/14174 in (Desai) view of Muller US 5, 858, 410 (Muller).

Desai et al (Patent WO '174) discloses a process for preparation of microparticles or nanoparticles of water insoluble drugs; e.g. paclitaxel, an agent that is insoluble in water and uses polymers such as polylactides and polyglycolides. The drug is dissolved in an organic solvent (page 17, lines l 5-25), a protein such as albumin is added to stabilize the nanoparticles (page 17, lines 31-34) and the mixture is homogenized under high-pressure homogenization (page 18, lines 6-15 and page 51, lines 25). In disclosing a method for making a pharmaceutically acceptable formulation, Desai discusses sterile-filtration and how drug of particle size less than 200 nm is obtained (page 19, lines 1-16, page 10, lines 24 and page 20, and lines 30-35). The drug particles can be in crystalline or amorphous for (page 13, lines 5-10); details of how to make drug particles of size less than 200 nm are provided. Furthermore, Desai

et al also disclose the effect the solvent used has on drug particle size (page 38, lines 5-20) and further discuss the advantage of making the composition in the form of albumin-paclitaxel combination-low toxicity.

Regarding the amendments to the claims, the dispersion which have water-reduced dispersion medium containing less than 80 wt% of water is disclosed in Example 4 wherein the taxol is dispersed in ethanol which is free of water i.e. 0% water.

Regarding reciting the limitation of "at temperature of 20°C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20°C to 25°C. Thus the instant claims temperature still overlap with the prior art.

Desai did not disclose the piston-gap homogenizer required in claims 44-47
Muller teaches a method for preparing nanoparticles of drugs e.g., corticoids such as prednisolone (col. 22, lines 40-45), the drug particles having average size of 10-1,000 nanometers made by dispersing solid therapeutically active drugs in a solvent and subjecting the dispersion to high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (i.e. under 90 degrees; col. 20, lines 35-40).

Instant claims reciting "water-reduced dispersion medium containing less than 50 wt% of water", the recitation would not distinguish the instant claims over the prior art because Muller teaches a method to make a drug carrier subjecting a solid therapeutically active compound dispersed in a solvent to high pressure homogenization in a piston-gap homogenizer to form particles having an average diameter of 40 nm to 100 nm wherein said active compound is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents (claim 38), note that the use of the preposition "or" means the exclusion of the aqueous media in the dispersion which is interpreted as a non-aqueous solvent and a percentage of 0%

water and consequently, less than 50%. Regarding including the limitation of "at temperature of 20°C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20°C to 25°C. Thus the instant claims temperature still overlap the range of the prior art.

In addition the amount of water of less than 50% is obvious over both Desai and Muller because Desai teaches paclitaxel is added to methylene chloride. The solution was added to human serum albumin solution. The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model: Tempest I) (Example 1). Further, Muller teaches the use of glycerol (example 4) while instant disclosure glycerol contains 0% water (see example 13, page 36 of the specification)

Therefore it would have been obvious to one of ordinary skill in the art to make paclitaxel nanoparticles according to the methods disclosed by Desai and homogenize it in a piston-gap homogenizer because Muller teaches that it is evident that by conversion of the microparticles into nanoparticles by means of a high-energy process increase the surface tension to such an extent that as a result the saturation solubility increases greatly (col. 6, lines 19+). The person of ordinary skill would have expected success of having a method of preparing nanoparticles of an insoluble or barely soluble active agent using a high pressure homogenizing process in a piston-gap homogenizer and containing less than 80% of water.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

**(10) Response to Argument**

- Appellant states that the entire specification of Muller requires the use of a large amount of water (about 80 to 99 % of water) as the dispersion medium in order to create cavitation and produce the particles. Muller teaches that the "dispersion principle is cavitation." Cavitation by

definition requires large amount of water and, thus, Muller teaches against using less water. At column 5, lines 27-28, Muller teaches that "Suspensions were prepared with a drug, which was ground in an air jet, in an aqueous surfactant solution." [Emphasis added.] The specification of Muller in fact teaches that the high pressure dispersion medium is water or an aqueous medium containing about 80 to 99 % of water. The Examiner has not, and cannot, cite any language in Muller that teaches to use less than 50 wt.% water in the dispersion medium. Dispersing particles produced by the water-based high pressure homogenization process of Muller thereafter in an organic solvent for further purposes cannot be read as a production of such particles in an organic solvent dispersion medium.

This was not found persuasive because **Desai, the primary reference teaches the reduced or no water dispersion in Example 4**. However, it is noted that nowhere in Muller, the reference teaches that there must be 80% to 99% of water to achieve the reduction of particle size. In addition, Muller is relied upon for teaching high-pressure homogenization using a piston-gap homogenizer (abstract and col. 20, lines 23-30). Regarding Appellant's arguments that column 5, lines 27-28 which Appellant cites and which states "suspensions were prepared with a drug, which was ground in an air jet, in an aqueous surfactant solution"; the citation is limited to one embodiment. However, the reference is considered for all what it pertains and not only for the cited lines. Also Muller teaches literally that "since the **lowest possible surfactant content is desirable** from the toxicological aspect, surfactant-free nanosuspensions have also been prepared" (col. 8, lines 27+). Thus, Muller teaches to reduce the aqueous surfactant disclosed. In addition, Muller teaches different embodiments wherein there may not be the aqueous surfactant argued. Further, the reference discloses that reduction of particle size in mills is possible if the viscosity of the dispersion medium is increased but the speed of rotation must remain constant (col.3, lines 21+).

- Desai did not disclose the use of water in the process of making the particles in different embodiments (see example 1) which teaches 30 mg paclitaxel disssolved in 3.0 ml human serum albumin soltion (1% w/v)", has no factual basis. Example 1 of Desai on page 33 clearly discloses that 30 mg paclitaxel is dissolved in 3.0 ml of methylene chloride, which solution is added 27.0 ml of a solution of human serum albumin having a concentration of 1% w/v. This mixture is finally high pressure homogenized using an Avestin homogenizer. Thus, the major component of the dispersion medium is indeed water (90%). Moreover, the use of serum albumin as such is not the critical point. The critical point is that Desai uses it in form of a 1% w/v solution, and thus always introduces a high amount of water into the dispersion medium prior to the homogenization.

This was not found persuasive Appellant ignores Example 4 of Desai which teaching 30 mg Taxol is dissolved in 0.55 ml chloroform and 0.05 ml ethanol. The solution is added to 29.4 ml of Tween 80 solution (**1** % w/v), which is presaturated with 1% chloroform. The mixture is homogenized for 5 minutes at 25 low RPM (Vitris homogenizer, model: Tempest I. **Q.)** in order to form a crude emulsion, and then transferred into a high pressure homogenizer (Avestin). Thus, Appellant argument of about 90% or 85% does not exist in all examples of Desai and therefore, Desai teaches reduced or exclusion of water during homogenization. Further, it is noted that Desai also teaches a high pressure homogenizer (see for example page 14, line 20) and that instant specification which is concerned with high pressure homogenization of reduced water dispersion discloses the Avestin homogenizer (see instant spec., page 20, line 4) which is the same homogenizer disclosed by Desai. Thus, even Avestin homogenizer of Desai is expected to achieve the same results required by instant claims. However, since Desai did not specify the piston-gap type, Muller is relied upon for this disclosure.

- Desai teaches away from using higher amounts of organic solvents. As can be seen from Example 7 of Desai at page 38, an alteration of the organic phase fraction showed that increasing the phase fraction led to a significant increase in particle size. Even a shift from 2% to 3% to 4% resulted in a particle size increase from 150 nm to 200 nm to 250 nm, which teaches to those skilled in the art that a further shift to an organic phase fraction of more than 50% would be expected to result in particle sizes well above the limit of the claimed invention. Thus, there is the clear teaching in Desai not to use dispersion media having a low (less than 85%) or even no water content.

This was not found persuasive because the increased particle size produced by increasing the organic phase fraction is still less than one micron. Note that the instant claims require particle size of 5.6 micron. Therefore, even increasing the organic phase fraction as shown in example 7, Desai still produced an acceptable particle size that is less than one micron (note that independent claim 1 requires particle size distribution of less than 5.6 microns). In addition, the reference does not teach away because Desai teaches in the (abstract) that the procedure yields particles with a diameter of less than about 1 micron and that the use of specific composition and preparation conditions (e.g., addition of a polar solvent to the organic phase) and careful selection of the proper organic phase and phase fraction, enables the reproducible production of unusually small nanoparticles of less than 200 nm diameter. Thus, the reference does not teach away since Desai recognized that increasing the diameter of the particle has a good possibility by increasing the organic phase fraction. It is respectfully noted that the use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain. *In re Heck*, 699 F.2d 1331, 1332—33, 216 USPQ 1038, 1039 (Fed. Cir 1983). Finally, Appellant asserts an amount of 85% or more of water relying on Desai's example

7 although the reference is relied upon for all what it pertains and not only one example. Appellant's assertion also ignores Muller '410 which teaches in the (abstract and claim 29) the possibility of using non-aqueous medium for dispersion.

- It is not a simple matter to change from one homogenizing device to another, such as from Desai's Avestin homogenizer to the claimed piston-gap homogenizer, without considering also the other requirements for such devices, in particular the homogenization medium. There is no disclosure in any of the cited documents which might invite a person of average skill in the art to modify their teachings in such a way that the presently claimed process would be obtained.

This was not found persuasive because at the time of the claimed invention, such homogenizers were well known in the art and were known for making designed particles relying on different factors which obviates the instant subject matter (for e.g. using gold for rings and ear rings would not exclude gold from being a hair pin). In addition, instant claims recite "reduced water"; thus, the claims do not exclude water for avoiding cavitation. Also, cavitation is recited in the instant claims as an inherent result of the homogenization process. Since the prior art teaches the same dispersion and homogenizer, the same result thereof would be expected to occur. Further, Muller teaches using cavitation or shearing and impact forces with introduction of a high amount of energy (abstract). Thus, Muller teaches a method that may produce or avoid cavitation (see abstract of Muller '410). Regarding modifying Desai by using the piston-gap homogenizer disclosed by Muller '410, it is noted that Desai teaches generically high pressure homogenizer (see for example page 14, line 20) and that Avestin homogenizer which is used by Desai include piston-gap homogenizers for example, Avestin C-50 is a high pressure homogenizer of the piston-gap type. Thus, even Avestin homogenizer is expected to achieve the same results required by instant claims. Thus, the person having ordinary skill in the art

would be motivated to modify the generic type homogenizer disclosed by Desai because Muller teaches that it is evident that by conversion of the microparticles into nanoparticles by means of a high-energy process, to increase the surface tension to such an extent that as a result the saturation solubility increases greatly (col. 6, lines 19+).

- Appellant argues that the Examiner's statement at the top of page 12 of the Final Office Action, it should be noted that the teachings of Muller with respect to cavitation and shear forces has to be divided. The cavitation effect is related to the use of a piston- gap homogenizer, while the shear and impact forces are related to other devices such a microfluidizer or nanojet using the jet stream principle. See column 4, lines 16-21, and column 5, lines 6-7, respectively. Since the claimed method requires the use of a piston- gap homogenizer, the mention of shear and impact forces related to other devices in Muller are of no relevance.

This was not found persuasive because at the top of page 12 (the last page of the office action), the Examiner was responding to Appellant's argument that "the surprising results produced in the instant disclosure is the use of piston-gap homogenizer in combination with high pressure homogenization medium having a dramatically reduced content of water resulting in dramatically decreased cavitation effect". It is also noted that Appellant's arguments now and then ignores the following:

- Muller's teaching that cavitation is not the only approach to reach the nanoparticles required
- piston-gap homogenizer is the same high pressure homogenization and it is not a combination of two.
- Instant claims do not recite dramatically decreasing cavitation but require no cavition "without cavitation", see claims 46 and 47.

Finally, although Appellant argues that the mention of shear and impact forces related to other devices in Muller are of no relevance, the Examiner asserts that the response is relevant because it demonstrates that the shear and impact forces is an alternative method to cavitation (which requires water in the dispersion), please see claim 39 of Muller which recites

> ".... the active compound has an increased saturation solubility and an increased rate of dissolution compared with powders of the active compound prepared using an ultrasonic probe, a ball mill or a pearl mill, the solid particles having been comminuted, without prior conversion into a melt, by using cavitation or shearing and impact forces with introduction of a high amount of energy, and wherein said active compound comprises at least one compound selected from the group consisting of: analgesics, anaesthetics, antirheumatics etc.

It is clear that shear and impact forces are alternatives to cavitation.

- In page 9 of the arguments, Appellant states that the goals of the current invention are met by way of a unique and surprising combination of features:
    - an anhydrous or considerably water reduced (less than 50% water) dispersion medium instead of mainly water, and in combination
    - a piston-gap homogenizer instead of other homogenization devises such as a micro-fluidizer.

The Examiner finds the statement contradicting with the instant specification which discloses the equivalent use of high-pressure homogenizers of the piston-gap homogenizer type such as piston-gap homogenizer type (APV Gaulin Systeme, French press, Avestin), jet-stream homogenizers (e.g. Microfluidizer), rotor-stator systems (Ultra-Turrax, Silverson homogenizers), ultrasound bath, ultrasound rod and ultrasound homogenizers (instant spec., page 20).

- None of the prior art can realize these benefits since none teach or disclose the use of an anhydrous or considerably water reduced (less than 50% water) dispersion medium and the use of a piston-gap homogenizer.

This was not persuasive because the prior art does not have to teach literally the reduction of the amount of water or using anhydrous dispersion. However, Muller '140 teaches in the abstract discloses "Provided is a drug carrier, comprising particles of at least one pure active compound which is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents". Note that "or" favors the meaning of organic solvents only.

Therefore, Desai teaches hardly soluble drugs in very low or no water dispersion homogenized in high pressure homogenizer (example 4). Therefore, claim 10-14, 16, 17, 32-34 and 44 are obvious over Desai in view of Muller.

Also, "without cavitation" is an inherent property to the same method. Since Desai teaches hardly soluble drugs in very low or no water dispersion homogenized in high pressure homogenizer (example 4) and Muller teaches 0% water (abstract) and piston-gap type high pressure homogenizer and the resulted particles of the drugs are in the same size, then there should be no cavitation. Thus, claim 46 and 47 are obvious over Desai and Muller.

Desai and Muller did not disclose the temperature under freezing, however, Appellant did not show unexpected results of homogenization in a temperature under freezing point of water (Appellant discussed the unexpected results of the claimed invention in the remarks dated 11/13/2009 stating that the use of a piston-gap homogenizer in combination with high pressure homogenization medium having reduced content of water or even with no water content cause the unexpected results, see remarks, page 15, last paragraph). The recitation of the under freezing temperature is not described in any detail or used in the examples to show unexpected results. Thus, claims 24, 39, and 40 are obvious over Desai in view of Muller.

Regarding the recitation of gentle particle size reduction with minimization of the impairment of the chemical stability of the homogenized material, Desai teaches the stable

homogenized material all through the disclosure for example (page 12, lines 10+) and Muller teaches the long-term stability of the of the nanosuspensions, see for example (example 9). Thus, both references teach the reduction of particle size and the stability of the homogenized material. However, the word "gentle" is an inherent property of the method. Therefore, claims 27 and 45 are obvious over Desai and Muller.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/NABILA G EBRAHIM/

Examiner, Art Unit 1618

Conferees:

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